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CHILDREN'S HOSPITAL

WASHINGTON, D. C.

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INFANTILE CORTICAL HYPEROSTOSES

(CAFFEY-SMYTH SYNDROME)

Case Report No. 122

Frederic G. Burke, M.D. R. G. 46–4410

R. G., a 3½ month old white male infant, was first admitted to Children's Hospital on May 25, 1946, with the chief complaint of fever and irritability. The illness had begun one week previously with a swelling about the right side of the face. This was associated with irritability, which, together with the fever, continued on up to the hospital entry. The day before admission the temperature rose to 105°F., at which time the child seemed to have some twitchings of the arms and legs, but there were no frank convulsions. The past history revealed the child had had some difficulty with his formula at the age of 4 weeks and also had has some mucus and blood streaks in his stools. The formula was adjusted several times, and the stools became normal. The baby gained weight in a normal fashion. Vitamin supplements had been administered in adequate amounts since the age of 4 weeks.

The family history revealed that the patient's paternal aunt had had active tuberculosis six years previously and that she had been in a sanatorium where a pneumothorax and phrenicectomy were done. Allegedly, her infection has been inactive for the past four years. She took care of the baby for four to five days during the second week post-partum and wore a mask during this time. She had also visited the baby intermittently since then. The child's mother had always had negative chest x-rays and sputum until two or three weeks previously when a chest x-ray was thought to show some calcification in the right lung. The mother had had several episodes of pleurisy since the age of 16. A sputum examination done on the mother shortly before the infant's admission was negative for tubercle bacilli.

Physical examination at the time of admission revealed a well-developed, well-nourished 3½ month old infant who appeared acutely but not critically ill. The temperature was 104.4°F. There was a swelling on the right side of the face which extended superiorly to the upper level of the ear and down to the angle of the jaw. This area was tender and indurated but nonfluctuant. There was no inflammation of Stensen's duct and no palpable calculi. The liver and spleen were palpable one finger breadth below the costal margin. The heart and lungs were negative, and the remainder of the physical examination was essentially normal.

Laboratory examination showed a hemoglobin of 8.5 gm. with 3.2 million

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red cells; the white cell count was 14,100 with 66 per cent polymorphonuclear cells, 29 per cent lymphocytes, 3 per cent monocytes, and 2 per cent eosinophiles. Platelet count was 150,000. Subsequent repeat hemograms showed a consistent leucocytosis ranging between 13,000 and 16,000 with an essentially normal differential. Urinalysis was negative. Examination of the spinal fluid was negative as were the febrile agglutinins. An x-ray of the chest revealed a pericardial shadow in the third to fifth interspace on the left, the nature of which was not known. Roentgen examination of the bones of the face revealed no evidence of periostitis at this time. Complement fixation test for mumps performed at the National Institute of Health was reported as negative. A tuberculin test (O.T. 1:1,000) was done, and within twenty-four hours an area of erythema measuring 2 cm. in diameter was observed. However, this erythema subsided so that at the end of forty-eight hours it was only minimally present. A repeat tuberculin test (O.T. 1:100) was negative, and P.P.D. No. 2 similarly showed no positive reaction. Gastric washings for tuberculosis organisms were performed at this time, and of five consecutive examinations, four were positive for tubercle bacilli on smear, while culture of the washings on Petragnani's media grew out tubercle bacilli on three occasions. A provisional diagnosis of primary tuberculosis was made on the strength of these positive gastric washings.

During the course in the hospital the child's temperature fell gradually during the first week and then remained low grade. The swelling upon the right side of the face subsided somewhat but did not completely disappear, and it remained quite tender. The baby took his formula moderately well and gained weight. Therapy during this admission consisted of penicillin (20,000 units every three hours for seven days) and then sulfadiazine for four days. However, neither drug appeared to exert any favorable influence on the course of the disease. He was discharged after a twelve day hospital stay to be followed in the dispensary.

At home the child continued to have a low-grade fever and was moderately irritable. The swelling of the right side of the face remained and occasionally became more marked. About two weeks after discharge it was noted that the left side of the face was becoming similarly involved. One week later a painful tender swelling was noted along the left forearm. An x-ray of the long bones taken at this time showed a periostitis along the shaft of the left ulna at the distal end, and it was thought that this lesion represented a tuberculous periostitis. The child was then readmitted to the hospital for treatment with streptomycin.

Physical examination at this time revealed a fretful 4 month old infant who appeared chronically ill. Both sides of the face showed a marked, brawny, tender edema extending from the lower lobe of the ear to the angle of the jaw (Fig. 1). Stensen's duct did not seem to be involved. There

was a diffuse swelling and marked tenderness along the distal end of the left arm. Heart and lungs were negative. The liver and spleen were palpable one finger breadth below the costa margins. The rest of the examination was essentially negative. The temperature was 102.6°F.

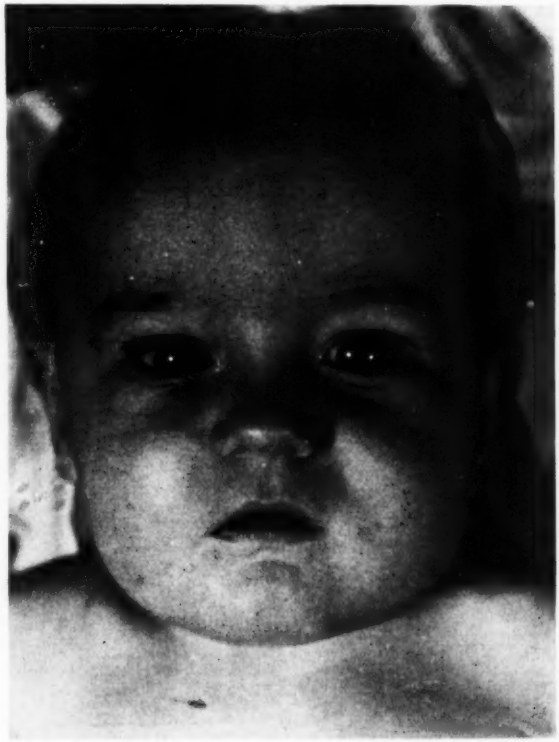

FIG. 1. R. G. at the time of readmission to the hospital. Note the marked bilateral facial edema.

Laboratory examination revealed a hemoglobin of 10 gms. with 3.5 million red cells; the white count was 27,000 with 53 per cent polymorphonuclear cells, 46 per cent lymphocytes, and 1 per cent eosinophiles. Repeat urinalyses were negative. The blood culture taken shortly after entry was sterile. Sedimentation rate was normal. A gastric washing performed prior to the initiation of streptomycin therapy revealed a rare acid fast bacillus on smear. X-ray examination of the long bones of the upper and

lower extremities revealed some periosteal thickening of the bones of the upper extremities with some increase in the width of the distal portion of the ulna (Fig. 2). X-ray examination of the chest revealed no essential change since the previous film taken on May 29. Roentgenologic examination of the skull in the anteroposterior and lateral positions revealed no definite evidence of abnormality. Wassermann and Kahn tests were nega-

FIG. 2. R. G. X-ray of the extremities reveals a periosteal lamellated thickening of the long bones.

tive. Serum calcium was 11.5 mg. per cent and phosphorus was 3.3 mg. per cent. The ascorbic acid level was 0.369 mg. per cent. A blood sample was sent to the National Institute of Health for complement fixation virus studies and was found to be negative.

On June 27, the day before the second admission, the patient was started on streptomycin with a dose of 30,000 units every three hours intramuscu-

larly. For the first two weeks in the hospital the temperature remained elevated in the neighborhood of 101° to 102°F.; subsequently it came down to normal by lysis, and the child remained afebrile during the remainder of his hospital course. The patient slowly gained weight, and his appetite remained moderately good. The bilateral facial swelling gradually diminished and had completely disappeared within two and one half weeks. Swelling and tenderness of the ulna also subsided progressively and disappeared in approximately the same interval of time. The sedimentation rate, which had been normal at the time of entry, rose to 39 mm. per hour (Winthrobe) within two weeks and remained substantially elevated (ranging between 22 and 45 mm. per hour) during the next month in the hospital. Repeated white counts showed a leucocytosis varying between 9,000 and 22,000 with the neutrophiles ranging from 17 to 60 per cent. While on streptomycin therapy, repeat gastric washings were obtained for tubercle bacilli, and with the exception of one washing on July 11 which yielded a rare acid fast bacillus on smear, all the other specimens, eleven in number, were negative both on smear and culture.

Within three weeks after admission, repeat x-ray examinations of the left ulna revealed evidence of healing of the periostitis noted at the time of admission. On August 12, x-ray examination of the thorax revealed some periostitis of the left clavicle and of the fifth rib anteriorly and the eighth rib posteriorly, similar in effect to the lesion involving the left ulna. A re-examination of the mandible on August 22 revealed a rather diffuse periostitis bilaterally on the inferior surface of the mandible. X-ray of the left ulna taken on August 28 just before discharge showed continued resorption of the previously described periosteal proliferation. On August 11 an exacerbation of the edema of the face was noted bilaterally and was quite tender and swollen. There was no concomitant temperature elevation, and the facial swelling subsided gradually during the course of the next three weeks with only slight residual ton-tender swelling remaining on the left side. Streptomycin was discontinued on August 17 after forty-seven days of therapy; the amount of drug administered totaled approximately 12 million units. No untoward effect from streptomycin was noted during the interval of its administration.

On August 22, one week prior to discharge, the sedimentation rate had returned to normal and the patient appeared clinically well. The infant was discharged on August 29, after a two month stay in the hospital.

Follow-up x-ray examinations during the next six months showed continued and progressive healing of the previously noted areas of periostitis of the left ulna, clavicle, ribs, and mandible. The facial edema has completely disappeared, the temperature has remained within normal limits, and the infant appears completely well.

DISCUSSION

Sidney Ross, M.D. This patient represented a diagnostic problem for a considerable period of time and probably would have remained so had it not been for the fortuitous simultaneous publication of a paper by Smyth, Potter, and Silverman[1], in which were reported seven cases of a new syndrome which bore a striking similarity to our case. In common with our patient, the patients of Smyth and his associates showed marked irritability, fever, anemia, periosteal involvement and a characteristic brawny, tender facial edema. There was little doubt following this report that our case fitted into this syndrome. Since attention has been called to the entity, nine additional cases of this syndrome have been diagnosed during the past eighteen months at Children's Hospital; two of the cases have been culled from our hospital records by reviewing all charts of infants under 6 months who had a discharge diagnosis of scurvy; a re-examination of their x-rays together with a review of the protocol indicated rather unequivocally that both cases were examples of this new disease entity. A detailed account of these cases will be discussed in a forthcoming report[4].

In 1945 Caffey and Silverman[2] first described four cases of this syndrome, which they termed infantile cortical hyperostoses, presenting the symptoms previously noted. The basic roentgen change as described by Caffey was an external thickening of the corticalis, which was lamellated in many instances. Bones involved included the mandible, clavicle, scapula, ribs, and extremities. The soft tissue swellings preceded the formation of the hyperostoses in the neighboring bones and have occurred in the face, thorax, and extremities. The active manifestations in Caffey and Silverman's patients subsided completely after several weeks with no serious complications.

In spite of the general objections to eponyms in medical nomenclature, we have referred to the syndrome as Caffey-Smyth disease in our cases at Children's Hospital in view of the obscure etiology of the syndrome. In addition, it has been our impression roentgenologically that the skeletal lesion was primarily a periosteal reaction rather than a cortical involvement.

Thus far there has been a total of seventeen cases of this syndrome reported in the literature[1–3]. Of these, thirteen infants were under 7 months of age. The ten cases of Caffey-Smyth syndrome diagnosed at Children's Hospital during the past eighteen months have similarly all been in children under 7 months of age.

A compilation of the findings in the thirteen infants under 7 months of age reported by Caffey and Smyth is set down in Table I. As will be noted, the feeding history including vitamin supplements was adequate in every case. Fever and irritability as well as the characteristic brawny, tender, nonhyperemic facial edema were noted in all patients but one.

TABLE 1

A compilation of the findings in the thirteen infants under 7 months of age reported by Caffey and Smyth

CASE NO.	SEX	AGE OF ONSET	FEEDING HISTORY	FEVER	IRRITABILITY	BRAWNY EDEMA OF FACE	W.B.C.	TUBERCULIN TEST	VIT. C LEVEL	SEROLOGY	SEDIMENTATION RATE	OUTCOME
									mg %			
1	F	5 mo.	Adequate	+	+	+	16,000–24,000	Neg.	0.12	Neg.	Elev.	Recov.
2	F	5 mo.	Adequate	+	+	+	12,000	Neg.	0.10	Neg.	Elev.	Recov.
3	M	7 mo.	Adequate	+	+	+	14,000–20,000	Neg.	0.085	Neg.	Elev.	Recov.
4	F	3 mo.	Adequate	+	+	+	23,000	Neg.	.44	Neg.	Elev.	Recov.
5	F	4 mo.	Adequate	+	+	+	23,000–37,000		1.35			Recov.
6	M	2 mo.	Adequate	+	+	No	13,000	Neg.	Low blood, high urine	Neg.	Elev.	Recov.
7	M	2 mo.	Adequate	+	+	+	6,000			Neg.	Nor.	Recov.
8	M	2½ mo.	Adequate	+	+	+	14,000	Neg.		Neg.		Recov.
9	M	3 wk.	Adequate	No	No	+		Neg.		Neg.		Recov.
10	F	4 mo.	Adequate	+	+	+	13,000	Neg.		Neg.	Elev.	Recov.
11	M	2 mo.	Adequate	No	No	+	11,000–21,000					Recov.
12	F	4 mo.	Adequate	+	+	+						Recov.
13	M	3 mo.	Adequate	+		+	7,000–29,000	Neg.		Neg.		Recov.

The white cell count was increased in the majority of instances, and there was usually a lymphocytic predominance. The tuberculin test as previously noted was negative in every patient where it was performed in the series reported by Caffey[2, 3] and Smyth[1]. (In the case reported here the tuberculin was equivocally positive, but all our other nine patients had negative tuberculin tests.) Vitamin C levels were not singularly aberrant. Similarly the serology was negative in all patients. In the majority of instances where it was performed, the sedimentation rate was elevated. The periosteal skeletal involvement was widespread, as will be noted in Table II. The mandible was involved in every patient but one and accounted for the frequency of the brawny edema of the overlying soft tissue of the face; the latter was by far the most striking presenting symptom and

TABLE II

A compilation of the site of periosteal involvement in the thirteen patients under 7 months of age reported by Caffey and Smyth

CASE NO.	MANDIBLE	CLAVICLE	SCAPULA	RIBS	EXTREMITIES
1	+	0	0	+	0
2	+	+	0	0	+
3	+	+	0	0	+
4	+	0	0	+	0
5	0	0	0	0	0
6	+	+	0	+	+
7	+	0	0	+	+
8	+	+	+	+	+
9	+	+	+	0	+
10	+	+	0	0	+
11	+	0	0	0	0
12	+	0	0	0	+
13	+	+	0	0	0

permitted a provisional diagnosis to be made on sight in the majority of cases. The clavicle and extremities were other frequent sites of periosteal involvement. In one case seen at Children's Hospital, the only bony involvement was noted in the left scapula.

The etiology of this new syndrome remains obscure. Scurvy has been considered in the differential diagnosis in view of the periosteal bone involvement. However, the usually noted scorbutic bone changes, such as the zone of rarefaction beneath the epiphyseal line, the ground-glass appearance of the shaft, the Wimberger rings, and the absence of any subperiosteal hemorrhage on biopsy, would militate against a diagnosis of scurvy. In addition, the age of the onset of the syndrome (i.e., mostly 3 to 4 months) as well as the history of adequate vitamin C intake and lack of response to vitamin C would similarly be against a diagnosis of scurvy.

As for an infectious etiology, which is suggested by the increased white blood count, fever, and elevated sedimentation rate, there is not too much definitive evidence. Blood cultures and febrile agglutinations were negative in all cases, and there was no perceptible response to sulfonamides or penicillin. Biopsy specimens have similarly not been in keeping with a diagnosis of an infectious process. Smyth[1] and Caffey[2,3] mention that virus studies were not done in their cases. However, complete virus studies were performed at the National Institute of Health in five out of our ten cases, and all were negative. Syphilis can be ruled out on the basis of negative serologies, both in the patients seen at Children's Hospital as well as those reported by Caffey[2,3] and Smyth[1]. As for tuberculosis, we were initially under the impression that we were dealing with an acid-fast infection in the case reported here, in view of the positive gastric washings and history of exposure to tuberculosis. However, the generalized periosteal involvement was unlike the bony lesions described in tuberculosis, and, more important, the subsequent nine patients have had negative tuberculin tests and repeated negative gastric washings. Similarly in the seventeen cases described by Caffey and Smyth, tuberculosis was rather effectively ruled out. We can only conclude that the tuberculous infection in the present patient was co-existent and coincidental and was unrelated to the syndrome.

The possibility that the lesion may be of a sarcomatous nature as suggested by the laminated periosteal reaction is ruled out by the benign course of the disease together with the absence of any evidence of sarcoma on biopsy. Similarly, traumatic ossifying periostitis seems to be excluded. The disease at its onset may similarly be confused with parotitis as well as osteomyelitis of the mandible and neoplasm of the mandible.

In every case reported thus far as well as in our own ten cases, the disease was benign and ran a self-limited albeit a protracted course, sometimes lasting for months. The excessive irritability, slow weight gain, and poor feeding habits of the infant make this disease a sore trial for the parents. However, a good prognosis can be categorically given in every case once the diagnosis is made.

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PERICARDITIS WITH EFFUSION

Case Report No. 123

Elmer Fantazier, M.D. M. M. 48–731

M. M., a 5 year old white girl, was admitted to this hospital on January 19, 1948 with the chief complaint of fever and pallor.

The present illness began five days prior to admission when she complained of nausea and felt unusually warm. She vomited following breakfast and was unable to retain food for forty-eight hours. There was no diarrhea. The symptoms slowly subsided during the ensuing forty-eight hours, and the patient was allowed limited activity. On the morning before admission it was noted that the child was listless and had developed considerable pallor. On the day of admission she complained of pain in her left chest on movement, and the pallor was increased.

The past history revealed that the patient was the product of a nine months' gestation and an uneventful delivery. Her birth weight was 7 pounds. The neonatal period was not remarkable. Measles occurred at 4 years, from which she made a slow but uneventful recovery. The mother stated that the patient had had "flu" last winter, from which the convalescent period was about three weeks.

The family history revealed that there were two siblings, both living and well. There was no history of familial or constitutional diseases.

Physical examination showed a poorly nourished white girl who appeared acutely ill. The temperature was 100°F., and the pulse was rapid and thready. The blood pressure was 88 systolic, 58 diastolic. The skin was very pale and moist; no petechiae or rashes were noted. Palpable cervical nodes were present. The pharynx was moderately injected, and a thick white exudate was noted on the right posterior pharynx. There was a questionable friction rub over the lower left lung field anteriorly. The heart was enlarged to the left on percussion, and the sounds were muffled, distant, and rapid. No murmurs were heard. The liver was palpable three finger breadths below the costal margin. The spleen was not felt. A fecal mass was palpated in the left lower quadrant of the abdomen. No abnormalities of the extremities were noted, and the reflexes were physiologic.

An x-ray taken shortly after admission showed the heart to be enlarged to the right and left (Fig. 1). The cardiac contour was "water bottle" in type, indicative of dilatation and some pericardial effusion.

A blood count on admission showed a hemoglobin of 12 gm. with 3.9

million red blood cells; the white count was 16,900 with 85 per cent polymorphonuclears, 8 per cent lymphocytes, and 7 per cent monocytes. Urinalysis was negative, as was the tuberculin patch test.

On the day of admission the patient was seen in consultation by Dr. Bernard J. Walsh.

The patient was given sulfadizine initially in a dose of 7.7 gr. every four hours, and Digifolin, 1½ gr. three times a day, but she began to vomit the

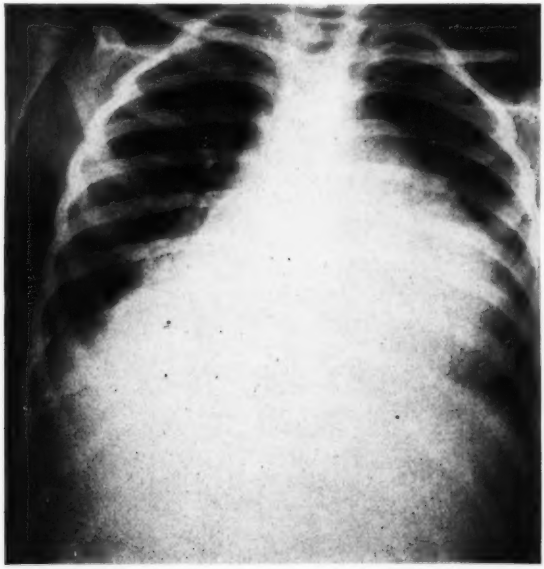

FIG. 1. M. M. X-ray of the heart taken on admission revealing considerable cardiac enlargement to the right and left. The cardiac contour has a "water bottle" appearance suggestive of pericardial effusion.

medications after the third dose of sulfadiazine. She was then given an infusion of 200 cc. of 5 per cent glucose in saline slowly over a period of an hour, and penicillin was substituted for the sulfadiazine.

The child was fluoroscoped twice within twenty-four hours after admission. Following the second fluoroscopy, a pericardial tap was done by Dr. Walsh, and 200 cc. of fluid were obtained; the first 20 cc. were clear yellow, while the remainder of the fluid was a medium brown color. Following the pericardial tap there was considerable clinical improvement.

Analysis of the pericardial fluid obtained from the tap was as follows:

	Light fluid	*Dark fluid*
Cells	5,000	8,000
R.B.C.	13%	8%
W.B.C. polymorphonuclears	77%	91%
Lymphocytes	6%	1%
Mononuclears	4%	1%

Specific gravity: 1.018
Smear and culture of fluid: Negative

The patient has been on penicillin, 50,000 units every three hours intramuscularly, since the onset of vomiting on the second hospital day. She

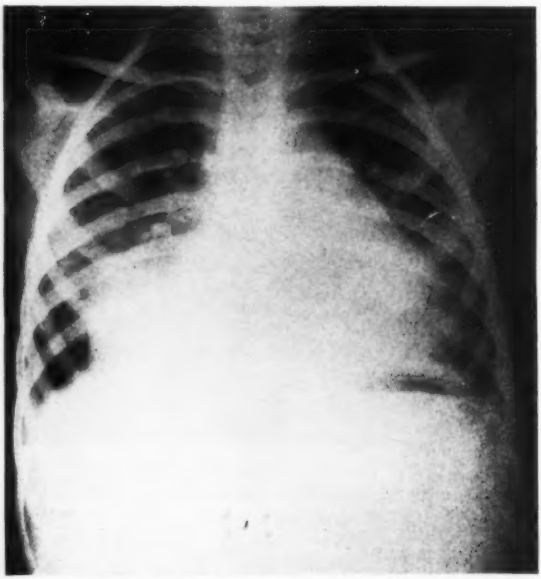

FIG. 2. M. M. X-ray of the heart taken at the time of discharge showing some reduction in the cardiac-pericardial size. Subsequent fluoroscopy two and one half weeks later showed the cardiac contour to be normal in size and shape.

also has received a maintenance dose of 8 minims of tincture of digitalis by mouth daily. The child is taking fluids well and eating soft foods now. The temperature has remained at about 100° to 101°F. since the pericardial tap on January 20, 1948.

Clinically the patient has shown steady improvement. The heart con-

tinues to be enlarged on the left on percussion, but the heart sounds are more readily heard.

A chest film taken on the day of discharge is shown (Fig. 2). As seen by repeated fluoroscopic examinations, there has been considerable reduction in the cardiac-pericardial size. The pulsations along the cardiac borders gradually increased in amplitude. The liver enlargement slowly receded and became less tender. She was discharged on February 2, 1948.

DISCUSSION

Bernard J. Walsh, M.D.: When I first saw this patient shortly after her admission to the hospital, I found her lying flat, in no respiratory distress,

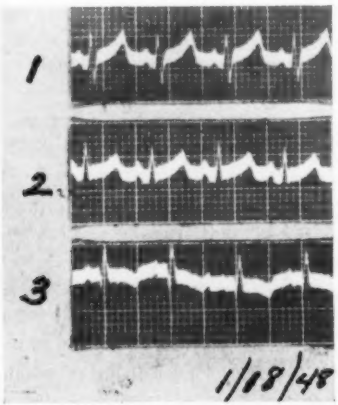

FIG. 3. Ecg. showing slight elevation of S-T segments and T Lead I

and with moderate facial pallor. There was no edema or cyanosis of the extremities. The cardiac rhythm was normal. There was no gallop. I was unable to hear any sounds indicative of friction rubs, either pericardial or pleural. No murmurs were heard. The heart sounds were moderately distant. The area of cardiac dulness was considerably increased, extending to about the anterior axillary line in the fourth and fifth left interspaces. There was a flat note on percussion with distant breath sounds over the lower third of the right chest posteriorly. The liver was smooth and slightly tender and the edge was readily felt three finger breadths below the costal margin in the right midclavicular line.

The electrocardiogram (Fig. 3) was within normal range, although there was very slight elevation of the S-T segments in Lead I consistent with acute pericarditis.

Fluoroscopic examination showed a large cardiac-pericardial shadow with very poor to absent pulsations on all borders. The enlargement was chiefly to the left. There was a wedge-shaped density at the cardiohepatic angle on the right, the nature of which was not clear, but it seemed more consistent with fluid in that area than with pneumonic infiltration.

A siagnosis of acute pericarditis with pericardial effusion, cardiac tamponade, and possible myocardial failure was made.

In view of the possibility that some degree of heart failure was present, digitalis was recommended.

Late on the second hospital day I again saw the patient, and it was apparent that she had grown worse. She was in no particular respiratory distress and was able to lie flat, but she looked much more ill and her facial pallor had increased. The liver had further enlarged. A pericardial tap was done immediately, the needle being inserted in the fifth interspace, approximately 1.5 cm. inside the left border of cardiac dulness. The first 20 cc. of fluid were light yellow and clear. The remainder of the fluid was dark amber. It was believed that the difference in color resulted from pocketing of the fluid. When about 100 cc. of fluid had been withdrawn, the patient seemed much improved. When she was returned to her room, it was apparent to all who had seen her before the pericardial tap that she was materially better. Her liver became much less tense and diminished in size by 1.5 to 2 cm.

Pericarditis due to any cause is unusual, both in children and in adults. It is not rare in children, however, this patient being the third we have had in this hospital in the past six months. The cause of the pericarditis, even when there is a good deal of pericardial effusion, remains unknown in the majority of our cases. Pericarditis associated with rheumatic fever makes up approximately 30 per cent of the cases of acute pericarditis we have seen in this hospital. Another 10 per cent of the patients have purulent pericarditis due to the influenza bacillus, the pneumococcus, or to other organisms. After the diagnosis of pericarditis is made, the next most important decisions concern effusión. If effusion is present, is it causing increasing restruction of the heart? Is it purulent, or not? If there is a leucocyte count of 20,000 or over, and particularly if there is a temperature of 103°F. or more, I believe a purulent pericarditis must be strongly suspected, and it is best to do a pericardial tap. If the effusion is purulent, it is seldom possible to remove the pus except by surgical drainage. If the patient with pericarditis has a large liver and/or orthopnea, even though high fever and considerable leucocytosis are absent, cardiac tamponade can be considered practically certain. It is our practice to observe such patients carefully for increase in the size of the liver and increase in the

size of the cardiac-pericardial shadow. If increase is noted by comparison with the first examination, then a pericardial tap is carried out and as much fluid as possible is removed. However, pericardial tap, either because of possible purulent pericarditis or increasing cardiac tamponade, needs to be done only occasionally. In the vast majority of patient, the infection subsides over a period of six or eight weeks, accompanied by steady decrease in the size of the liver and in the amount of fluid in the pericardium.

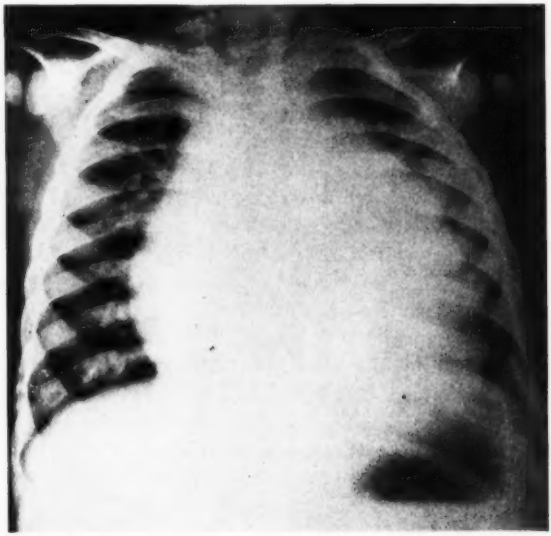

FIG. 4. J. M. 16 month old child with acute pericarditis with effusion. X-ray of the heart at the time of admission revealed a considerably enlarged cardiac-pericardial shadow. The cardiac size subsequently returned to normal.

The x-rays (Fig. 4) show a large cardiac-pericardial shadow in a 16 month old child who was on the medical service here recently. The second film was taken when the child was ready to leave the hospital. The etiology remains unknown for this patient also. It was not necessary to tap the pericardial sac. This is the youngest patient I have ever seen with pericarditis. I have seen her recently in the Cardiac Clinic, and she is now well, leading an active normal life. The cardiac-pericardial shadow has returned to normal. The cardiac pulsations are vigorous in all views by fluoroscopic examination.

Addendum: February 18, 1948: The patient was examined today. She has been eating well and has no complaint. She has seemed to her parents to be quite her usual self. On examination she appeared in good health. The cardiac rhythm, rate, and sounds were normal. The heart sounds were vigorous and loud. There was no edema or cyanosis. There was no enlargement of the liver. Fluoroscopic examination showed a full-sized, normal appearing heart with very vigorous pulsations except in the region of the right auricle.

ACTINOMYCOSIS WITH PULMONARY INVOLVEMENT

Case Report No. 124

Robert C. Garby, M.D. L. S. 40-3815

L. S., a 9 year old negro girl, was admitted to Children's Hospital on December 14, 1947, with the chief complaint of a "knot in her throat." Recently she had been fairly well until about ten days prior to entry when she had a cold accompanied by a non-productive cough and marked malaise, and stayed in bed. The cough was aggravated, and there was some dyspnea while lying flat on her back. Her neck had been stiff for three days, and the night before admission pain was noticed in the neck.

The past history revealed that her first admission to the hospital was on June 29, 1945, for gonorrheal vaginitis, which was treated with penicillin with good results. She was discharged on July 11, 1945, thirteen days after admission. Her next hospital admission was at Gallinger Hospital of this city on January 14, 1946. The diagnosis of left lobar pneumonia was made. She showed marked toxicity during the first week of her hospital stay. The temperature fell by lysis, being normal on the sixth day and her chest cleared slowly. X-rays showed considerable pneumonic infiltration on the left side. Clubbing of the fingers and toes was noticed at that time.

The next hospital admission was on August 1, 1946, when she had a "knot on left shoulder," had had a cold and cough for several weeks, and her fingers and toes had been swollen for one week. Physical examination at that time showed a firm, fixed, non-tender mass protruding from the left chest anteriorly. There was dulness to percussion lateral to the mass and scattered dulness in the left chest posteriorly. Moist rales were heard throughout the left chest with increased breath sounds and scattered rales in the right lung. The fingers and toes were clubbed.

Laboratory examinations revealed a hemoglobin of 12 gm., with 4.3 million red blood cells and 11,300 white blood cells with 65 per cent neutrophiles (58 per cent segmented and 7 per cent stab cells), 3 per cent eosinophiles, and 32 per cent lymphocytes. The urine was clear and acid, with a specific gravity of 1.020, albumin 5 mg. per cent, and many white blood cells in clumps.

Repeated blood examinations through August 14 showed a leucocytosis ranging between 11,000 and 17,000 with essentially similar differentials. Repeated urinalyses were essentially negative. No Bence-Jones protein was found. Repeated sputum cultures, concentrated smears, and gastric washings for tuberculosis were negative. Fluid aspirated from the mass on the chest showed a hemolytic Staphylococcus aureus on one culture,

and on another examination a fungus was found which the National Institute of Health considered to be a nonpathogen and probably an air contaminant.

Treatment consisted of 20,000 units of penicillin intramuscularly for three days, and again six weeks later 50,000 units of penicillin intramuscularly every three hours were given for forty-eight hours for a return of the gonorrheal vaginitis. The cough gradually cleared over a period of two months, the x-rays cleared somewhat, and she was discharged on November 10, 1946, to be followed as an outpatient.

Her developmental history showed that she did not walk or talk until the age of $2\frac{1}{2}$ years, and her dentition was markedly delayed. Cod liver oil and orange juice intake was believed to have been deficient. For several years she has had epileptoid seizures lasting five to ten minutes during which she "sees" her mother who died of a "nervous breakdown."

Physical examination on the day of her present hospitalization revealed a chronically ill, poorly developed, and poorly nourished child. The temperature was 100.4°F. and respirations 20. There was a tender swelling about the size of a small lime in the suprasternal region, which was fluctuant, moderately fixed, and did not move on swallowing. Congestion of the nasal mucosa was present, and the tonsils were inflamed and hypertrophied. Examination of the lungs revealed increased dulness over the left lower lobe. On deep palpation of the abdomen, slight tenderness in both lower quadrants was present. There was a shallow, indolent-appearing ulcer over the left side of the sternum, surrounded by a dark, leathery discoloration about 3 cm. in diameter. There was marked clubbing of the fingers and toes, as well as cervical, axillary, and inguinal lymphadenopathy.

Laboratory examination of the blood revealed a hemoglobin of 9.5 gm., 3.9 million red blood cells, 11,500 white blood cells, and 79 per cent neutrophiles (72 per cent segmented and 7 per cent stab cells), 1 per cent eosinophiles, and 20 per cent lymphocytes. Sedimentation rate (corrected) was 34 mm. per hour. On December 20, 1947, the blood sugar (fasting) was 83 mg. per cent; Kahn and Mazzini tests for syphilis were negative; an ECG was interpreted as being within normal limits.

On December 27, 1947, microscopic examination of material obtained from aspiration of the swelling in the neck was found to be typical of actinomycosis. Biopsy of a left axillary gland was done on December 22, 1947, and was reported as chronic hypertrophy; no actinomycosis was seen. One routine blood culture done here was negative. A blood culture for fungi which was done at the National Institute of Health was negative. Total blood protein shortly after admission averaged about 9 mg. per cent, and the albumin-globulin ratio was reversed, averaging 0.6/1. Gastric washings for actinomycosis have been negative thus far.

A chest x-ray on the day after admission (Fig. 1) was interpreted as follows: "Examination of the chest reveals the cardiac contour to be 'water bottled' in shape with a loss of the cardiophrenic angles and enlargement to the right and left of the entire silhouette. This has the appearance of pericardiac effusion with cardiac enlargement. The interlobar fissure is

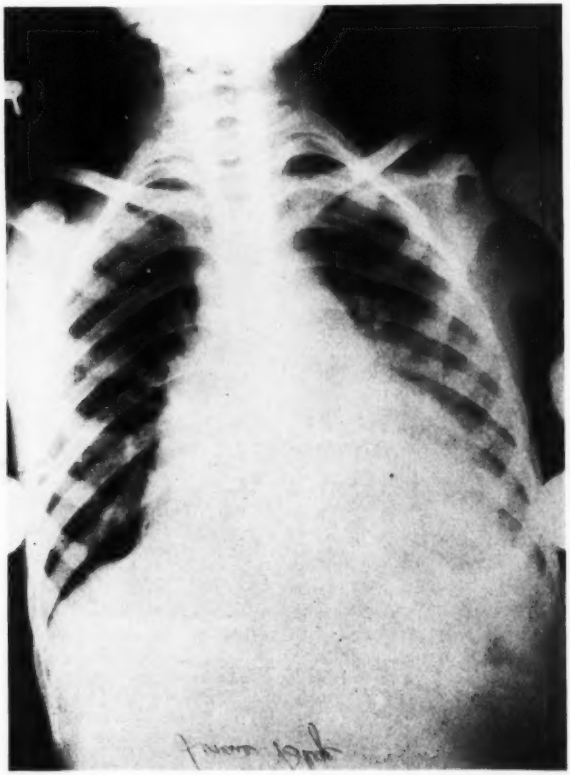

FIG. 1. L. S. Actinomycosis of the lung and pericardium

thickened on the right and contains a little fluid, and there is some low-grade infiltration in the lower half of the left lung. Chronic granulomatous disease with cardiac involvement should be ruled out." Four days later another report reads: "Fluoroscopic examination of the chest in the upright, prone, and head-down positions reveals a definite increase in the supracardiac shadow in the head-down position. This represents some pericardial fluid though not enough for pericardial tapping. . . ."

On February 6, 1948, the x-ray report reads: "Re-examination of the chest by fluoroscopic and radiographic techniques reveals adequate pulsations of fair amplitude of the heart. . . . There is considerable reduction in the size of the cardiac silhouette. There is some reduction in the amount of infiltration, and at the present time there is some fibrosis and calcification at the roots." The last x-ray report on February 10, 1947 "reveals the cardiac silhouette to be even smaller than at the previous examination. . . ."

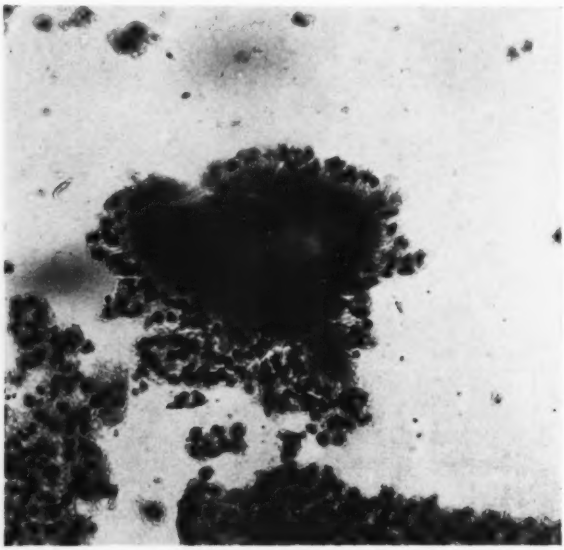

FIG. 2. L. S. Microscopic section revealing the typical sulphur granules of mycelial growth characteristic of *A. bovis*.

Sulfadiazine, one gram every four hours, was begun on December 27, 1947, when the diagnosis was established. After the gastric washings were obtained, penicillin, 100,000 units every three hours, was begun on January 12, 1948, many sulfonamide crystals were found in the urine, and sulfadiazine was discontinued and Citra-Sulfa was substituted. High protein diet, whole blood transfusions, intravenous plasma, and supplementary vitamins have completed the therapeutic measures.

During the first month of the patient's hospital stay the temperature ranged irregularly from normal to 100° or 101°F. daily. Since that time it has decreased to a maximum of about 99.8°F. daily (rectal). Objectively and subjectively there has been marked improvement with considerable increase in strength, brightening of the mental picture, and disappear-

ance of the cough. The suprasternal abscess ruptured on December 18, 1947, drained for about two weeks, and then closed and has remained closed. The chest lesion has apparently healed completely, leaving considerable scar formation.

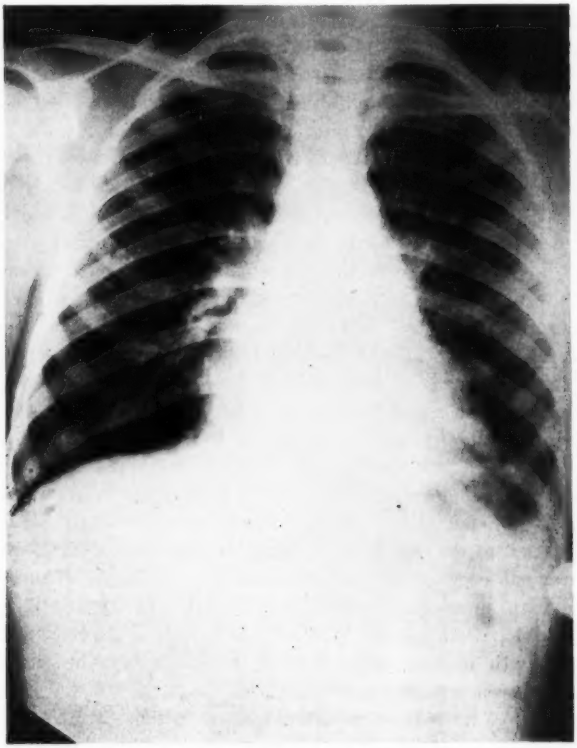

FIG. 3. L. S. Actinomycosis showing marked clearing from the parenchyma and pericardium. There is still considerable fibrosis at the roots.

Follow-up note, February 29, 1948: Clinically this child continues to show vast improvement and response to treatment. This is reflected by the chest film (Fig. 3). She still continues to evidence a low-grade fever, however, with a temperature of about 100°F.

DISCUSSION

Thomas Bradley, M.D.: This case illustrates several characteristic features of actinomycotic infections of the lungs and chest wall. First,

there is evidence that the lesion is of quite long duration. In June of 1945 the child was admitted to Children's Hospital with gonorrheal vaginitis, at which time it was noted that there were coarse rhonchi during inspiration. There was no clubbing of the fingers at that time. She was given oral penicillin doses of 20,000 units every three hours for ten days. It is not unreasonable to suppose that the fungus infection was present at that time and that it was possibly affected by the treatment. About six months later she was treated in Gallinger Hospital for lobar pneumonia with sulfathiazole, and at that time clubbing of the fingers was noted. She was discharged from Gallinger Hospital after twenty-three days of treatment with residual changes in the base of the left lung which were thought to be due to pneumonia. She was again admitted to Children's Hospital in August of 1946 with a definite suspicion that actinomycosis was the cause of the persistent lung pathology, but a careful search for the fungus was unsuccessful. Poppe reports that in nineteen cases seen at the Barnes Hospital the diagnosis was not made in several cases until two or three years of intermittent study had been made.

The advent of chemotherapy has brightened the outlook in actinomycotic infections, but it must be remembered that patients recovered in some instances prior to the use of these drugs. In 1911, Harbitz reported eighty-seven cases of actinomycosis involving the thorax and lungs with 100 per cent mortality. In 1930, Good of the Mayo Clinic reported that this type of infection was almost uniformly fatal. Two years later, Wangensteen commented on the fact that all cured patients except one had had some form of surgery, such as rib resection, drainage of abscesses, and thoracoplasty.

Poppe reports on nineteen patients seen in the Barnes Hospital over a period of years, in seven of whom the disease was apparently arrested. In these seven patients, some type of rather radical surgery was used in conjunction with either x-ray, thymol, penicillin, or the sulfonamides. Iodide therapy was not used in these cases.

Apparent cures have been reported from a variety of medications, and it is probably true that the situation is somewhat analogous to the treatment of pulmonary tuberculosis. Proper combinations of surgery to drain secondarily infected abscesses with chemotherapy offer good results if the patient is seen early enough.

Just which drug is best is not completely clear, but the best results have been obtained recently with penicillin, or with a combination of penicillin and sulfonamides. Abrahams and Miller report that penicillin has a greater inhibitory effect in in vitro experiments than sulfathiazole or sulfadiazine. Strains of *Actinomyces israeli* recovered from human subjects were grown in glucose nutrient agar containing varying concentrations of sulfathiazole and sulfadiazine. Some growth-inhibitory effect was noted

in levels of from 10 to 20 mg. per cent, but the effect was thought to be too slight for much therapeutic use. On the other hand, penicillin definitely inhibited growth in levels of 0.1 and 0.2 unit per milliliter of medium. This level is within therapeutic range in human beings.

Since actinomycosis is a disease characterized by long latent periods, followed by recrudescence, it is justifiable to state that several years should elapse before the disease is called cured rather than arrested.

To sum up the attitude of most clinics at the present, the following can be said:

1. Pulmonary actinomycosis with involvement of the chest wall is no longer to be considered a hopeless disease.

2. Therapy should consist of a varied attack. Abscesses should be adequately drained; rest for the patient and for the involved area in particular should be utilized.

3. Some patients will respond to internal medication alone, but this should not be relied upon to violate established surgical principles. The medical and surgical treatment of tuberculosis is analogous.

4. At the present, penicillin probably offers the best chance for cure. The simultaneous use of sulfadiazine helps with secondary invaders which may be resistant to penicillin.

*Chester W. Emmons, M.D.:** I have seen this patient only once before and have little to add to the discussion. The diagnosis of actinomycosis in this patient rests upon the demonstration of actinomycotic granules from one specimen obtained by aspiration of one of the subcutaneous lesions. I saw the section of this material only under a moderate magnification, and while it appears to me to be typical of actinomycosis, I should like an opportunity to examine a Gram-stained section with an oil immersion lens to rule out the possibility that this is a granule of, for example, staphylococcic actinophytosis (botryomycosis). However, this has no doubt been done in the hospital laboratory.

It would be helpful in confirmation of the diagnosis if cultures could be isolated. Since the lesions were not draining and sputum was not available when I saw the patient a week ago, we made cultures from the venous blood on the improbable chance that there had been a hematogenous spread and that actinomyces still might be present in the circulating blood. This occurs in rare cases, but the cultures in this case have remained sterile.

I think that the clinical course in this patient has not been typical of actinomycosis. If the patient has had pulmonary actinomycosis since the onset of the present illness, it would be expected that a draining sinus tract would have developed through the thoracic wall. I understand that there

* Principal mycologist, National Institute of Health.

was no x-ray evidence of continuity between the pulmonary lesion and the substernal abscess, although x-rays were taken during and at the height of development of the latter. Both the subcutaneous lesions have ceased to drain now. Is it possible that these lesions followed hematogenous or lymphatic dissemination from a transitory maxillary lesion? It would be desirable to continue attempts to obtain sputum, and to study additional gastric washings in order to shed more light on the nature of the pulmonary lesions.

Since pulmonary actinomycosis has such a grave prognosis, it is surprising to see this patient in her present condition. Therapy so far has not been directed toward actinomycosis, as I understand, and penicillin and other drugs she has received in the past have not been given in sufficient amounts and over long enough periods of time so that a response would be expected in actinomycosis. It may be, however, that the penicillin she has received has been of some benefit, and since several reports during the past three years have indicated that actinomycosis responds to penicillin therapy, its continued use in this case seems justified.

E. Clarence Rice, M.D.: The aspirated material from the fluctuant mass was smeared and cultured, and no mycelial elements were found. It was only after some of the material was placed in formalin and paraffin sections prepared that the typical granules of mycelial growth were found (Fig. 2). These are the typical "sulphur granules" seen in infections due to *Actinomyces bovis.*

This is the second case of actinomycosis which we have had at Children's Hospital. In othe other patient the actinomyces were found in a biopsied specimen.

On a number of occasions we have found similar bodies in the crypts of removed tonsils when sections were examined microscopically. This apparently is not an uncommon finding, and these bacteria are probably saprophytes.

ACUTE REGIONAL ENTERITIS

Case Report No. 125

George William Ware, M.D.

D. D., an 8 year old white boy, was admitted to Children's Hospital, on the service of Dr. William O'Donnell, on November 24 complaining of a sore throat. Two weeks previously a diagnosis of scarlet fever had been made, for which sulfadiazine and later penicillin were given. A papular rash appeared a week before admission and persisted.

Family history and past history were negative except for a pyloroplasty at the age of one month.

Physical examination upon admission revealed a young boy who was acutely ill and in obvious discomfort. The buccal and pharyngeal membranes were fiery red in appearance. The right tonsil was covered with an exudate. A papular rash was present over the extensor surfaces of both arms and legs and the entire face, and was noted to blanch on pressure. The remainder of the physical examination including the abdomen was negative. Urinalysis revealed 15 mg. of albumin, a trace of acetone, and on microscopic examination there were a few white blood cells with clumps. The red blood count was 3.6 million with 9.5 gm. of hemoglobin. The white count was 12,300 with 80 per cent neutrophiles, of which 64 per cent were segmented forms, 14 per cent band forms, and 2 per cent young forms. There were 16 per cent lymphocytes, 2 per cent eosinophiles and 2 per cent basophiles.

Penicillin therapy, 100,000 units every three hours, was immediately instituted and supplemented by the use of Elixir Benadryl. On the following day the temperature was 104°F. and pulse 120. The rash seemed to have improved somewhat. On the second hospital day the improvement continued, and the patient was placed on a soft diet. That evening he complained of abdominal pain of a generalized nature, which gradually increased in severity during the subsequent twenty-four hours. On the fourth day of hospitalization, the child commenced to vomit and had six watery bowel movements. The abdominal pain continued, and moderate diffuse abdominal rigidity with some distention became evident. The white blood cell count was now 13,700. The differential count showed 79 per cent neutrophiles (73 per cent segmented and 6 per cent band forms), 19 per cent lymphocytes, and 2 per cent eosinophiles.

The patient was seen in surgical consultation by Dr. Robert Coffey, and a diagnosis of ruptured appendix with diffuse peritonitis was made and an immediate operation advised. Preoperatively, 250 cc. Hartmann's solution containing 5 per cent glucose were given intravenously.

Under nitrous-oxide ether anesthesia, a lower right rectus incision was made. On entering the peritoneal cavity, a strikingly large amount of free serosanguineous fluid was encountered, 750 cc. being aspirated. The small bowel, beginning in the distal jejunum and terminating abruptly at the ileocecal valve, was of a fiery red color, slightly edematous, and the mesenteric nodes of the involved area were slightly but not notably enlarged (Fig. 1). The mesentery of the involved bowel was not appreciably thickened, and its vascularity did not appear abnormal. The cecum and appendix were not involved. After deciding against the removal of the

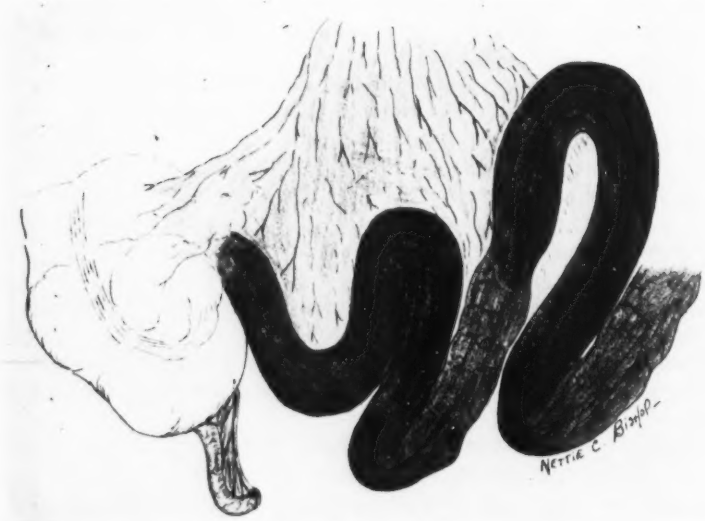

FIG. 1. D. D. Illustration showing the area of inflamed ileum proximal to its junction with the cecum.

appendix, the incision was closed in layers without drainage. Immediately after the termination of the operation the patient was given 250 cc. of whole blood intravenously.

The postoperative course was relatively uneventful. On the second postoperative day, urticarial wheals were observed on the upper extremities and over the abdomen, and the patient complained of severe itching in these areas. Rather prompt relief was secured by the use of benadryl. The white blood count at that time was 9,400 with a normal differential count. The platelet count was 244,000 per cubic centimeter. The patient was discharged from the hospital on the seventh postoperative day.

During the three month period since the patient's discharge from the hospital he has recuperated completely, a weight gain of 4 pounds has occurred, and he has no complaints referable to the gastrointestinal tract.

DISCUSSION

Robert J. Coffey, M.D.: Since the original description by Crohn and his associates[1] in 1932 of chronic regional enteritis, much has been learned about the clinical manifestations, course, and prognosis of this disease. It is essentially a disease of youth, involving in its chronic form any part of the jejunum, ileum, or right colon in a cicatrizing granulomatous process with a decided tendency toward the formation of internal and external fistulas. This chronic form of the disease is the one most frequently encountered and has been studied thoroughly. The acute manifestations of the disease, on the other hand, have seldom been studied pathologically since resection at this stage is seldom attempted. That such acute manifestations of the disease bearing his name did occur was well recognized by Crohn, and since then numerous cases have been reported. Erb and Farmer[2] pointed out that the occurrence of hemorrhagic edema of the ileum with conspicuous regional lymphadenopathy represents an early phase of regional enteritis and is characterized clinically by its similarity to acute appendicitis.

Whether all such cases of acute enteritis represent an early stage of chronic regional enteritis is a debatable point. Because of the occurrence of a rash preoperatively and the development of urticaria postoperatively, an intestinal anaphylactoid or allergic reaction was considered when the markedly hemorrhagic condition of the involved bowel with serosanguineous peritoneal fluid was observed. However, the sharply segmented area of involvement pointed to a true regional enteritis.

It has been suggested that true acute regional ileitis may be distinguished from nonspecific acute enteritis by the absence of enlarged mesenteric lymph glands in the latter[3]. However, since so little is known concerning the etiology and pathogenesis of acute regional enteritis, it seems illogical to apply any such criterion. Usually the involved bowel is reddened, thickened, and edematous, and the glands are conspicuously enlarged. Free peritoneal fluid is generally present and may be serous or serosanguineous. Cultures of this peritoneal fluid and of the involved mesenteric glands have been consistently negative. The terminal ileum is usually the site of maximal involvement, while the other areas in the jejunum, proximal ileum, or right colon may be affected in continuity or in a patchy manner.

Prior to Crohn's work, the acute form of this disease had seldom been described, and the chronic manifestations were usually considered to be tuberculous. This latter etiological factor has been definitely excluded

as a result of many studies[4]. The similarity of the pathologic manifestations in this condition to those found in Boeck's sarcoid have been interpreted as indicating a possible etiological relationship. Erskine[5] has observed the association of acute appendicitis and acute terminal ileitis in several instances and is of the opinion that both may be due to primary involvement of the mesenteric lymph nodes. This is in keeping with the experimental work of Reichert and Mathes[6], who were able to produce somewhat similar lesions in experimental animals by the injection of sclerosing solutions into the mesenteric lymphatics. However, subsequent investigators failed to substantiate these results.[7].

Since in its chronic form this disease occurs in early adult life, it is probable that the acute manifestations of the disease will be encountered in childhood and youth. Rose [3] refers to acute cases of the disease occurring in children of the ages of 5, 6, and 10. In the series of Fallis[8], the youngest patient in whom the chronic disease was identified was 9 years old. Koop and his associates[9] have recently reported a case of the chronic form of the disease in a newborn infant in whom the pathologic examination of the involved bowel revealed the typical changes of chronic regional enteritis.

The most important consideration in acute regional enteritis is the prognosis. Crohn[10] encountered eleven patients with the disease, of whom eight did poorly, six being eventually operated upon. However, most of the other reports have been less pessimistic in regard to the outcome[3, 11, 12], Smithy[13] feels that a spontaneous cure follows in most acute cases and that progression to the chronic form of the disease seldom occurs. A true picture of the ultimate outcome of these cases, however, depends on long and careful follow-up studies.

It is generally agreed at this time that in the chronic form of the disease a sidetracking operation, either with or without resection of the involved bowel, is necessary. There is similar agreement that conservatism should be employed when acute regional enteritis is encountered. Inasmuch as the majority of patients with the acute form are operated on under an erroneous diagnosis of acute appendicitis, the disease is identified on entering the peritoneal cavity. Since a spontaneous cure may be anticipated in the majority of early cases, surgical extirpation of the acutely inflamed bowel or a sidetracking operation is unwarranted. Removal of the appendix may eventuate in the development of a fecal fistula, a fact pointed out in a series studied by Coffey[14]. Mixter[15] and Fallis[8] advise against appendectomy, and certainly this procedure is undesirable if the cecum is involved.

The subsequent management of acute regional enteritis involves careful periodic observations plus recourse to roentgenologic study of the gastro-

intestinal tract in the event that suspicious signs or symptoms develop. It is our feeling that the use of intestinal chemotherapeutic agents such as succinyl-sulfathiazole or oral streptomycin is warranted for a month or six weeks following the identification of the acute disease.

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